Effect of Renal Hypertension in Sodium Deficient Rats on Juxtaglomerular Index and Zona Glomerulosa. (28269)

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There is evidence suggesting that excessive salt intake may be an etiologic factor in some instances of essential hypertension in man(1). Relatively prolonged dietary excess of sodium results in hypertension in the rat and its requirement for production of hypertension in this species after DOCA administration and adrenal regeneration is well established. The role of sodium in the pathogenesis of renal hypertension resulting from the application of a clip about the renal artery is less certain. Salt overload is unnecessary for its successful induction. Redleaf and Tobian(2) noted significantly less elevation of blood pressure in some rats on a sodium deficient diet, on which renal artery constriction and contralateral nephrectomy were performed, than in sodium fed controls, although a few did develop significant hypertension. Reduction of dietary sodium or administration of 1% saline as drinking fluid does not alter blood pressure in rats with established renal hypertension(2) although the latter has been observed to increase the incidence of hypertensive encephalopathy(3). There is convincing evidence that renal hypertension is related to the elaboration of renin by the clipped kidney. Yet, some effects of exogenously administered renin are enhanced by salt-priming(4).

This information has prompted the attempt to induce renal hypertension in sodium depleted rats. Evaluation of the degree of juxtaglomerular granulation (JGI), considered a reliable index of renin activity, might provide information concerning the nature of the consistently decreased JGI encountered in untouched kidneys of rats with renal hypertension. This decreased JGI has been attributed to increased blood pressure or renal perfusion (5) or salt retention mediated by the angiotensin-aldosterone mechanism(6). Salt overload(7) as well as an increase in renal perfusion pressure(8) have been observed to decrease JGI.

Methods. Sixty-eight adult female Wistar rats weighing 150-200 g survived the experimental period. Group A consisted of 12 subjected to sodium depletion by peritoneal dialysis 24 hours before partial constriction of the left renal artery. Ten comprising Group B were subjected to sham operation after dialysis. Partial renal artery constriction was performed in 10 non-dialyzed rats of Group C. Nineteen non-dialyzed, sham operated rats comprised Group D. Nine of Group E were treated similarly to those of A except that after 4 weeks of sodium deficiency, sodium was added to their diet. Ten of Group F were treated like those of B except that after 4 weeks they were subjected to sodium depletion.

Peritoneal dialysis was performed by withdrawal of 12 ml of peritoneal fluid 3 hours after instillation of 25 ml of 5% glucose in water. This resulted in removal of 10-20 meq/l of sodium. Dialyzed rats were maintained on a sodium deficient diet (General Biochemicals Co., Chagrin Falls, Ohio) and de-ionized water as drinking fluid. All other animals received the same diet containing 1% NaCl and tap water.

Blood pressure was estimated by a microphonic method prior to and at weekly intervals after operation. Animals of Groups A, B, C and D were sacrificed at 4 weeks by aortic puncture; those of Groups E and F 4 weeks after change in dietary sodium or 8 weeks after operation.

Kidneys were fixed in Helly's fluid and sections stained for estimation of JGI according to the method of the Hartrofts(7). Adrenals were blotted and weighed. Frozen sections were stained with oil red O after fixation in 10% formalin and width of the zona glomerulosa was expressed as percentage of cortex (ZGI).

Results. Sodium deficient rats subjected to renal artery constriction (Group A) exhibited a comparable degree of hypertension to that observed in rats maintained on a sodium diet

TABLE I. Effect of Na Depletion on Renal Hypertension, Serum Na and Cl, Adrenal Weight, ZGI and JGI.

	#	B P (mm Hg) Begin	B P (mm Hg) End	Serum (meq/l) Na	Serum (meq/l) Cl	Adrenal (mg)	ZGI	JGI UT*	JGI C†
A. Na deficient + clip	12	109 ± 15	140 ± 15	142 ± 4	106 ± 4	166 ± 20	14 ± 4	43 ± 19	85 ± 40
B. Na deficient	8	93 ± 8	102 ± 8	146 ± 13	110 ± 8	70 ± 21	13 ± 3	72 ± 28	
C. Na diet + clip	10	98 ± 9	135 ± 20	146 ± 6	108 ± 5	153 ± 17	8 ± 2	5 ± 4	38 ± 21
D. Na diet	19	92 ± 4	99 ± 13	144 ± 4	104 ± 10	62 ± 16	5 ± 1	24 ± 7	
E. Na deficient + clip + Na diet	9	98 ± 12	131 ± 12	146 ± 3	107 ± 5	96 ± 19	6 ± 1	7 ± 6	48 ± 17
F. Na diet + clip + Na deficient	10	96 ± 8	127 ± 22	141 ± 3	106 ± 2	92 ± 14	11 ± 1	18 ± 10	57 ± 8

* Untouched kidney. † Clipped kidney. ± Standard deviation.

(Group C) ($P>.1$) (Table I). Alteration of sodium intake after establishment of renal hypertension (Groups E and F) failed to influence the level of blood pressure ($P>.1$). JGI of clipped kidneys in all groups was greater than of untouched members ($P<.01$) and comparable to that of sodium deficient controls (Group B). JGI of untouched kidneys was statistically greater in sodium deficient hypertensive rats (Groups A and F) than in those maintained on the sodium-containing diet ($P<.01$) although less than that of sodium deficient controls (Group B) ($P<.01$).

Adrenals of all hypertensive rats were heavier than those of normotensive animals ($P<.01$). Sodium depletion did not affect adrenal weight. However, the ZGI of both hypertensive and normotensive sodium deficient rats was greater than that of rats receiving sodium ($P<.01$). Also the zona glomerulosa of the former was less sudanophilic.

Serum sodium was slightly but significantly ($P<.05$) reduced from normal only in those hypertensive rats subjected to sodium depletion before induction of renal hypertension (Group A) or after established renal hypertension (Group F).

Comment. Lack of statistical difference in degree of hypertension induced by unilateral renal artery constriction in sodium deficient rats and those maintained on the sodium-containing ration indicates that sodium is not essential for development of this form of experimental hypertension. As also noted by Redleaf and Tobian(2) sodium depletion had no appreciable effect on established renal hypertension induced in rats on a normal diet. Further, sodium repletion failed to influence the hypertension induced in sodium deficient rats during a 4 week period of observation. The lack of effect of sodium depletion on this form of renal hypertension is unlike that noted in the renal hypertension produced by renal compression in which sodium depletion is often accompanied by decrease in blood pressure(9).

Despite comparable degrees of hypertension in sodium deficient rats and those receiving sodium, significant differences in JGI were

encountered. Increased JGI in untouched kidneys of sodium deficient hypertensive rats and those subjected to sodium depletion following established renal hypertension is consonant with the recognized effect of sodium deprivation on JGI(7) and exhibited by sodium deficient controls in this study. Despite the increase, JGI was still statistically less than that observed in sodium deficient controls. This strongly suggests that JGI of untouched kidneys in rats with renal hypertension may principally reflect the sodium state of such rats and to a less degree pressor effects. This interpretation is not incompatible with the view that the juxtaglomerular apparatus represents a stretch receptor(5). The wider than normal zona glomerulosa of adrenal cortices and decreased JGI of untouched kidneys of hypertensive rats receiving the sodium-containing diet in this study are considered as evidence of sodium retention. It is of interest that the clipped kidneys of sodium deficient rats with renal hypertension also exhibited the effect of sodium deprivation. Their JGIs were for the most part comparable to those of sodium deficient controls.

The increased adrenal weight observed in all hypertensive rats is similar to the findings of Fregly(10) except that he did not observe any significant increase until blood pressures of 150 mm Hg or greater were encountered. Mean blood pressure of hypertensive rats in this study was slightly less. Although there was no significant difference in adrenal weight of hypertensive or normotensive sodium deficient rats and animals with comparable blood pressures maintained on sodium-containing diet, the width of the zona glomerulosa was conspicuously wider in the former which may be considered as morphological evidence for existence of the renin-angiotensin-aldosterone mechanism(11) in the renal hypertension encountered in sodium deficient rats.

Although acute sodium depletion was produced by peritoneal dialysis and animals were subsequently maintained on a sodium deficient diet, serum sodium was only slightly but significantly decreased in hypertensive animals subjected to such a procedure. Preliminary studies in our laboratory indicate that this method of depletion results in significant decrease in serum sodium for 5-7 days after which time values increase to normal or slightly below at 4 weeks. Elevated JGI and widened zona glomerulosa of adrenal cortices at this time however, are considered indicative of a sodium deficient state and have been noted previously in the presence of normal serum sodium in salt restricted rats(12).

Summary. Comparable degrees of renal hypertension were induced in sodium deficient rats and those receiving normal sodium intake following unilateral renal artery constriction. Sodium depletion had no effect on blood pressure of rats with established renal hypertension and similarly sodium supplement did not affect the renal hypertension of sodium deficient animals. JGI of untouched kidneys and width of zona glomerulosa of adrenal cortices in sodium-deficient hypertensive rats were greater than in those receiving sodium but less than those of sodium deficient controls. This suggests that changes in JGI of untouched kidneys of hypertensive rats primarily reflect the sodium state of the animals and to a less extent the effect of blood pressure *per se*.

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